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Cervical Cancer Screening for the Primary Care Physician

Clinical Practice Guideline
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"*These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations".*

General Principles: Since its introduction in 1943, the Papanicolaou (Pap) smear is widely credited with reducing mortality from cervical cancer and remains the mainstay of early detection of cervical intraepithelial neoplasia. Recently, increasing understanding of the role of high risk strains of the Human Papilloma Virus in the development of invasive cervical cancer, and the ability to test for these strains, has begun to affect the screening guidelines for cervical cancer. Despite these improvements, most invasive cervical cancers in the US are in women who have never been screened or have not been screened in the last five years, and these women are often in underserved patient populations. Technological advances in screening techniques will only offer a significant improvement in overall cancer incidence if they reach all women in the US.

1. Recommendations

Cervical Cancer Screening in Average-Risk Women

- **Method**: Screening should be done using either of the following cytological techniques as they have been found to have similar sensitivity and specificity for CIN2 or higher lesions
    - **Conventional Pap test:** using a broom-type (brush) device or plastic spatula and endocervical brush combination, smearing the cytological sample directly onto a microscope slide,
    - **Liquid based cytology** : The sample is collected as in the conventional Pap but then the brush suspends the sample cells in a fixative solution, disperses them, and then selectively collects cells on a filter. Liquid based cytology permits HPV testing to be done on the same sample.
    - In both cases, when two devices are used to collect the specimen, the ectocervical device should be used first.

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- **Screening Initiation and Periodicity**:
    - **The United States Preventive Services Task Force (USPSTF), American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) have all issued guidelines on cervical cancer screening. The ACS guideline recommends postponing the age for screening initiation to 25 and relying on HPV screening alone as the preferred methodology. MedStar Health endorses the USPSTF and ACOG recommendations.**
        - All average-risk women should begin cervical cancer screening at age 21, regardless of history of sexual activity or other risk factors. Cervical cytology screening prior to age 21 should be avoided. However, if women less than 21 years old are inadvertently screened, the guidelines for follow up and management of abnormalities for women aged 21-24 should be employed.
        - 21—29 years of age: Cervical cytology screening is recommended every 3 years. HPV testing—alone or with cytology- is not recommended in this age group.
        - 30-65 years of age: The *preferred* method is Cytology with high risk HPV co-testing every 5 years or HPV testing alone; Cytology alone every 3 years is acceptable.
        - >65 years of age: Cervical cytology screening may stop for those women with adequate screening history (Either 3 consecutive negative pap smear results, or two consecutive negative co-tests within the last ten years, with the last occurring within 5 years and no history of CIN2 in the last 20 years). Screening should not recommence for any reason, including having a new sexual partner. Following spontaneous regression or adequate treatment of CIN2, CIN3, or adenocarcinoma in situ, screening should continue *for 25 years*.
        - Post-total hysterectomy (removal of uterus and cervix): Cervical cytology screening may stop for those women **without** history of CIN2 or higher grade lesion, even if there is no history of adequate screening. Again, screening should not resume for any reason. For those women **with a history of CIN, AIS or cancer**, Pap smear screening via cervical cytology only should continue for 25 years regardless of whether the cervix is present or absent.
    - Women immunized against HPV: Continue to screen according to the age-specific recommendations for the general population.

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- Cytology more often than every 3 years and the use of cytology/high risk HPV co-testing more often than every 5 years for routine screening should be avoided.
- Testing for non-high risk strains of HPV has no utility in cervical cancer screening and should not be employed

	Age to Start	Method and Frequency	Age to Stop	s/p Hysterectomy
USPSTF 2018 and ACOG 2021	Age 21	Age 21-29: cytology q 3 yrs Age 30-65: cytology q 3 yrs or HPV testing alone q 5 yrs or co-testing q 5 yrs	Age 65 if adequately screened (3 neg cytologies or 2 neg HPV screens in prior 10 yrs, 1 of which in the past 5 yrs)	No need if cervix is gone and no h/o cervical cancer or CIN 2 or greater

Cervical Cancer Screening in High Risk Patients

HIV infected women, immunosuppressed women and women exposed to Diethylstilbestrol (DES) in utero are considered high risk. The ACOG and experts in cervical cancer research and care provide recommendations for screening in these populations.

HIV infected women and those who are immunosuppressed are less likely to clear HPV that is acquired (meaning it is more likely to persist) and pre-malignant cervical changes may progress more quickly to cervical cancer. Women considered immunosuppressed include:

- Recipients of solid organ transplants
- Recipients of allogeneic hematopoietic stem cell transplants
- Women with inflammatory bowel disease on immunosuppressant treatment
- Women with SLE
- Women with RA on immunosuppressant treatment

Cervical cancer in DES “daughters” is a non-HPV mediated condition. Consequently, screening relies on cytology rather than HPV testing. In addition to cervical cancer, DES daughters are at increased risk for cervical and vaginal clear cell adenocarcinoma.

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Cervical Cancer Screening in High Risk Patients

Condition	Screening onset	Modality	Frequency
HIV and immunosuppressed	Within 1 yr. of sexual activity	Cytology Or Cytology with HPV co-testing beginning age 30	Cytology—annually→q 3 yrs after three negative annual screens Co-testing—q 3 yrs after first negative co-test Continue screening throughout lifetime, stopping based on a shared discussion regarding quality of life and remaining life expectancy rather than age
DES exposed		Cervical and vaginal cytology	Annually until a woman is no longer a candidate for intervention

Results Classification System: Bethesda System

The Bethesda System was the creation of a standardized framework for laboratory reports that included a descriptive diagnosis and an evaluation of specimen adequacy.

Specimen Adequacy	
• Satisfactory • Unsatisfactory	
General Categorization	**Interpretation/Result**

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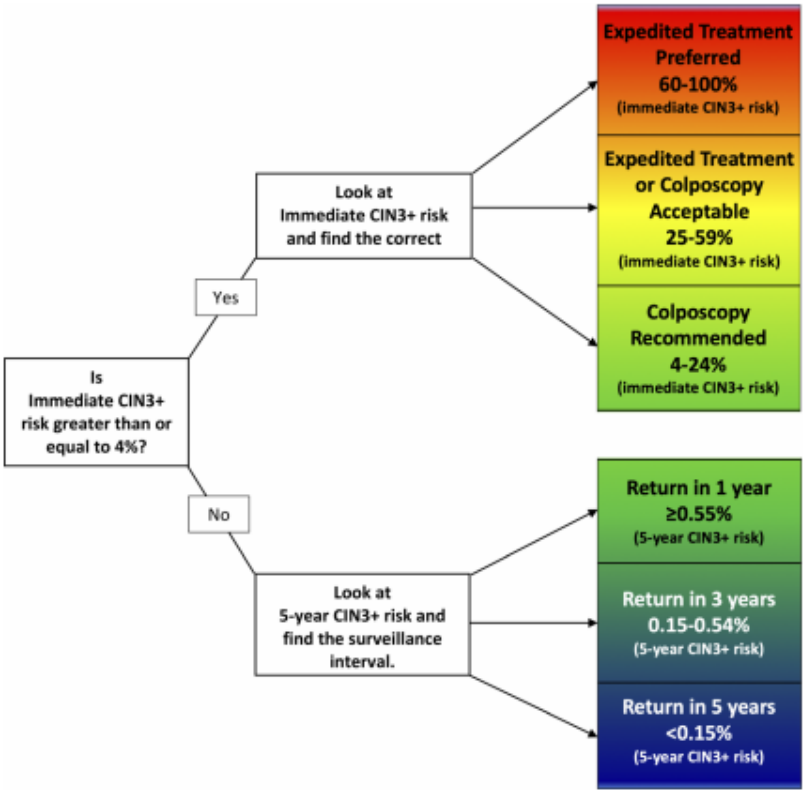
A. Negative for intraepithelial lesion or malignancy Includes: • "Within normal limits" • "benign cellular changes"	Organisms may be present including: • *Trichomonas vaginalis* • Fungal organisms morphologically consistent with *candida* species • Shift in flora suggestive of bacterial vaginosis • Bacteria morphologically consistent with • *Actinomyces* species • Cellular changes consistent with herpes simplex virus Other non-neoplastic findings (*optional to report; list not comprehensive*) Reactive cellular changes associated with Inflammation (includes typical repair) Radiation
B. Epithelial cell abnormality	**Squamous cell** • Atypical Squamous Cells of Undetermined Significance (ASCUS) • Low-grade squamous intraepithelial lesion • (LSIL) • Cannot exclude HSIL (ASC-H) • High-grade squamous intraepithelial lesion • (HSIL) • Squamous cell carcinoma
C. Glandular cells present	• Endometrial cells (may be benign or require further evaluation if post-menopausal) • Atypical glandular cells (AGC) may be atypical endometrial or endocervical cells • Atypical glandular cells, favor neoplastic

	• Adenocarcinoma in situ (AIS) • Endocervical adenocarcinoma in situ • Adenocarcinoma
D. Others	• Cases in which there are no morphological abnormalities in the cells per se; however, the findings may indicate some increased risk: for example, benign-appearing "Endometrial cells in a woman 40 years of age" • Other neoplasms identified, like small cell carcinoma

- **Follow up of abnormal Pap Smears—General Principles:**
  - **Current management guidelines have shifted from test results-based algorithms to guidelines based on the risk of CIN-3. Risk tables using patient age, current screening results and prior screening history have been developed and are accessible at http://asccp.org**
  - **In general, this risk based algorithm applies to women age 25-65.**



- **HPV test results are the basis for risk estimation**
- **Equal management is recommended for equal risk regardless of the combination of factors determining risk.**
- **Management recommendations include return to routine screening, 1 yr or 3 yr surveillance, colposcopy, or treatment**
- **An immediate risk of CIN 3 ≥ 4% requires referral for colposcopy or treatment**
- **A new abnormal screening test results following a negative HPV test or co-test within the past 5 yrs reduced the estimated CIN 3 risk by 50%**
- **The risk based management algorithm tool is accessible at https://app.asccp.org/**

Follow up of abnormal results outside the risk based strategy

The following clinical situations should be managed outside the risk based algorithm

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Follow up of Unsatisfactory Pap Smears:

- In cases where HPV is unknown (any age) or negative (age ≥ 25) age based screening should be repeated in 2-4 months.
- In those women 25 years or older where HPV is positive (unknown genotype), age based screening can be repeated in 2-4 months or the patient may be referred directly to colposcopy
- Women with a positive test for HPV 16 or 18 should be referred for colposcopy.

- **Follow up of Cytology Negative but Endocervical or Transformation Zone Lacking :**
  - Ages 21-29, routine screening
  - Ages 30-65, it is preferred that HPV testing be performed.
    - If the HPV is negative, the woman should undergo routine screening (the preferred co-testing in 5 years or the acceptable option of cytology alone in 3 years).
    - If the HPV testing is positive, Manage using the appropriate risk based guideline.
    - If HPV testing cannot be performed on the initial sample, cytology should be repeated in 3 years.

- **ASC-H on cytology:**
  - Refer for colposcopy regardless of HPV results since the rate of cancer is similar irrespective of HPV results

- **HPV 18 and HPV 16 positive, NILM (negative for intraepithelial lesion or malignancy):**
  - Refer for colposcopy

- **Two consecutive unsatisfactory screening tests:**
  - Refer for colposcopy

- **Pregnant woman:**
  - Pregnant women should be managed the same as non-pregnant women except endocervical curettage and endometrial biopsy are contraindicated ,and excisional biopsy should be performed only if cancer is suspected.

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- **Immunosuppressed patients of any age:**
  - Colposcopy is recommended for all results of HPV positive ASCUS or higher. If HPV testing is not performed on ASCUS results, repeat cytology in 6-12 mos is recommended with colposcopy for ASCUS or higher.

- **Women who have undergone hysterectomy for treatment of cervical abnormalities:**
  - Manage with 3 annual HPV based tests followed by long term surveillance with HPV based testing every three years for 25 yrs.

- **Women over age 65 with prior abnormalities:**
  - Manage according to the guidelines for women 25-65.

- **Women younger than age 25:**
  - Cytologic abnormalities in this age group are likely to represent non 16/18 HPV strains and have a high risk of regression and low risk of rapid progression to cancer. Management is therefore more conservative.
  - Low grade abnormalities (LGSIL, ASCUS with positive HPV or ASCUS without HPV) can be managed with repeat cytology at 1 and 2 yrs. After two negative cytology results, the patient can return to routine screening.
  - Colposcopy is recommended for high grade cytology at any time (HSIL, ASC-H, AIS) or for persistent low grade cytology at 2 yrs. ASCUS with reflex negative HPV can return to normal screening (cytology in 3 yrs). Expedites treatment is not recommended in this age group.

- **Patients with hysterectomy for benign disease:**
  - Screening is not recommended but ASCUS HPV positive and LSIL should be managed with follow up in 12 months.
  - HSIL, ASC-H, AGC should be managed with immediate vaginal colposcopy

Follow Up of Abnormal Pap Smear Results- 2019 Guidelines ASCCP

Result	Age	Follow up Step 1	Follow up Step 2
Unsatisfactory Cytology, HPV negative or unknown	All	Repeat ag based screening 2-4 months	Abnormal→ fu per guidelines Negative→routine screening per age guidelines Still unsatisfactory→colposcopy

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Result	Age	Follow up Step 1	Follow up Step 2
Unsatisfactory Cytology, HPV Positive	>=25	Either A) age based screening 2-4 months Or B) referral to colposcopy Women with HPV 16 or 18 should be referred for colposcopy	Abnormal→ fu per guidelines Negative→routine screening per age guidelines (since HPV+ this is co-testing one year, or if HPV 16/18 + → colposcopy) Still unsatisfactory→colposcopy
Cytology Negative but Endocervical Component or Transformation Zone Absent	21-29 Age 30-65— >=30 HPV unknown >=30 HPV negative >=30 HPV positive	Routine screening Add on HPV testing (preferred)Cytology in 3 yrs Routine screening Manage per risk based guideline	
ASC-H (atypical cells cannot exclude high grade lesion)	All	Colposcopy	

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Result	Age	Follow up Step 1	Follow up Step 2
Atypical Glandular Cells (including endometrial)	All	Colposcopy with endocervical sampling if not pregnant and endometrial sampling if ≥ 35 or< 35 and at risk for endometrial neoplasia	
ASCUS, LSIL, HSIL with or without HPV	25-65	Manage per risk based guideline	
ASCUS HPV +, ASCUS no HPV, LSIL	21-24	Repeat cytology at 1 and 2 yrs colposcopy for high grade cytology at any point; colposcopy if persistent low grade cytology at 2 yrs	
ASCUS HPV negative	21-24	Routine screening (cytology in 3 yrs)	
ASC-H/HSIL	21-24	Colposcopy	
Cytology negative, HPV Positive	>=30	Either a) Repeat co-testing 1 yr Or b) Genotyping for HPV 16/18	Cytology neg/HPV neg→ co-testing 3 yrs Ascus or higher or HPV pos → colposcopy Positive→ colposcopy Negative→ cotesting one year and follow guideline above
HPV testing alone-- positive	>=30	Test for HPV 16/18—colposcopy if positive Otherwise, reflex to cytology with colposcopy if ASCUS or higher Otherwise follow up 1 yr	

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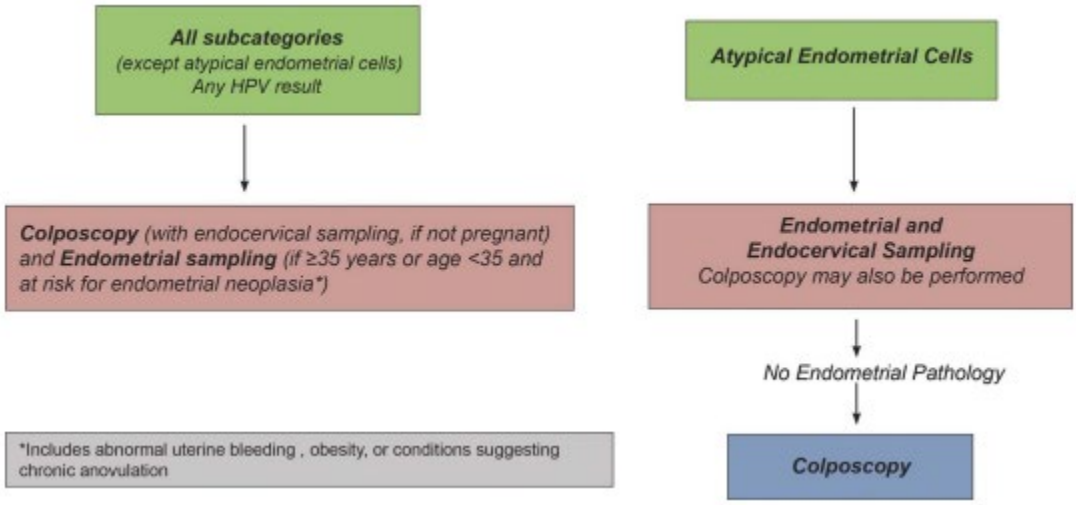
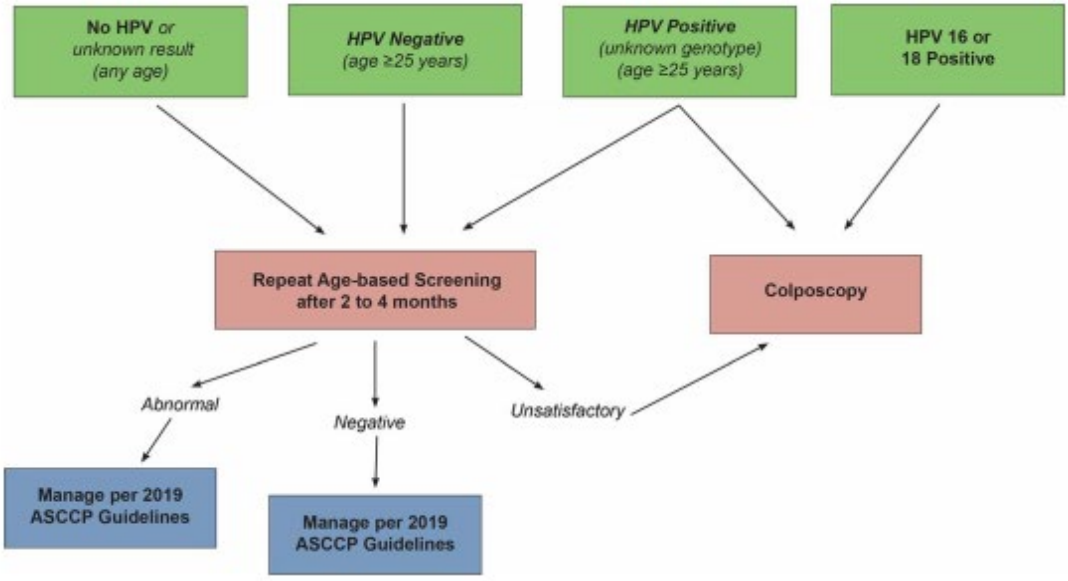
Work up of atypical glandular cells on cytology



Management of unsatisfactory cytology



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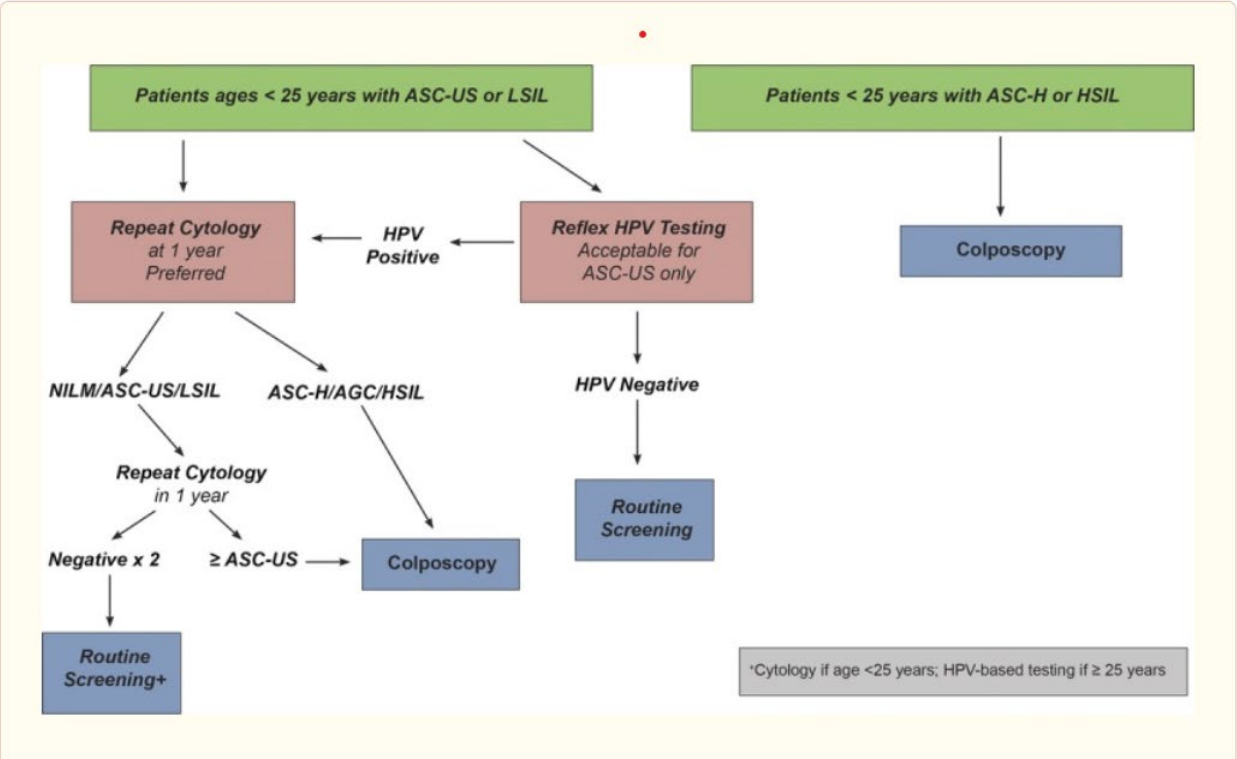
Management of results in patients younger than 25



Pelvic Exams when cervical cancer screening is not needed:

Both the United States Preventive Services Task Force (USPSTF) and American College of Obstetricians and Gynecologists (ACOG) state that there is insufficient evidence to recommend screening pelvic exams in asymptomatic women. ACOG recommends that pelvic exams be performed when indicated by medical history or symptoms and if, after a discussion of risks and benefits, the patient prefers the examination. Whether a pelvic exam is performed or not, discussion of reproductive and sexual health issues remains an important part of the health maintenance examination for women.

Patient Education/Counseling:
Suggested literature:
https://www.acog.org/Patients/FAQs/Cervical-Cancer-Screening

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Pamphlets (American College of Obstetricians and Gynecologists Online Bookstore): https://sales.acog.org/Cervical-Cancer-Screening-P464.aspx

JAMA Patient Page: August 21, 2018. Cervical Cancer Screening
https://jamanetwork.com/journals/jama/fullarticle/2697698

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